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CLINICOBACTERIOLOGICAL AND EPIDEMIOLOGICAL
FINDINGS IN PSEUDOTUBERCULOSIS OF MAN

(Dedicated to Professor E. Rodenwaldt on his 85th Birthday)

[Following is a translation of an article by Werner Knapp, Institute of Hygiene of Tübingen University, in the German-language publication Archiv für Hygiene und Bakteriologie (Archives for Hygiene and Bacteriology), No 147, Publishing House Urban and Schwarzenberg, Munich-Berlin, 1963, pages 369-380.]

Introduction: Ten years ago appeared the first report on abdominal clinical picture (Maschhoff, 1953; Maschhoff and Doelle, 1953) which presented the clinical symptoms of appendicitis, especially among children and adolescents, and showed a morphologically sharply pronounced affection of the lymph nodes. The morphological picture of this mesenterial lymphadenopathy induced Maschhoff to designate it as "purulent reticulocytary lymphadenitis", the etiology of which was clarified shortly afterwards by isolating *Pasteurella pseudotuberculosis* from excised mesenterial lymph nodes and by the demonstration of antibodies in the serum of surgical patients (Knapp and Maschhoff, 1954; Knapp, 1954). The morphological picture similar to tularemia, feline scabies (?) and inguinal lymphogranuloma caused Lennert (1961) to suggest "purulent reticulocytary lymphadenitis" as a defined morphological substrate for general classification and to differentiate it on the basis of the respective etiology.

Experience of recent years has shown that the demonstration of this morphological substrate and the complaints and symptoms apparently indicating an appendicitis call for a differential diagnosis of an infection with *Pasteurella pseudotuberculosis*. Through these observations, greater attention has been given also in human medicine to this long familiar pathogen of veterinary medicine and subsequent observations have been embodied in numerous reports from the clinic and the laboratory. Selected recent investigations form the basis of this communication which reports on further clinical-bacteriological and epidemiological findings during

recent years and gives some pointers on laboratory diagnosis under consideration of the experience acquired in bacteriological diagnosis.

I - Clinicobacteriological and Epidemiological Findings

1) Forms of the Disease: In human pseudotuberculosis, we distinguish between two forms of the disease:

a) Severe septic-typhoidal; b) enteric.

The earlier designation "appendicitic form" based on the clinical symptoms has been abandoned in favor of the designation "enteric form" because the appendix shows as a rule either none or only minor manifestations of the inflammation which were found primarily in the region of the ileo-coecal lymph nodes, the serosa of the ileo-coecal region, the wall of the distal ileum and of the caecum as the cause of the complaints resembling appendicitis.

The point of view of the pathologist in regard to human pseudotuberculosis has recently been thoroughly reviewed by Maschoff (1962) so that we need not enter on this aspect here.

a) Septic-typhoidal Form: Knapp (1959) has furnished the most recent review on the few cases in world-wide literature of this severe form which generally leads to exitus with toxic manifestations, icterus and coma. On the basis of a particular case, Knapp (1957) and Fischer (1958) stressed the necessity for extending routine serum reactions for the diagnosis of infections by *Salmonella*, *Shigella* and *Brucella* also to the diagnosis of the septic-typhoidal and enteric forms of human pseudotuberculosis. Individual examples show that indeterminate intestinal infections with non-characteristic due to *Past. pseudotuberculosis* repeatedly escaped an easily possible etiological clarification because of the absence of routine bacteriological-serological examinations and by reason of the frequently very early administration of antibiotics and sulphonamides in vague febrile affections. It is, therefore, today still impossible to estimate the frequency of the septic-typhoidal form.

It is probable that the observations, communicated in a brief note by Konrath (1960), on three children (aged respectively 15 and 24 months and 10 years) which were assumed to have died from the septic-typhoidal form should not be classified under this form. The antibodies demonstrated in non-saturated sera from two children with strains of *Past. pseudotuberculosis*, type II and/or IV (Moeskes 1960) do not permit any definite diagnostic conclusions (Knapp 1959; Daniels 1962) without cross-over saturation of the patients sera because of the antigen relations between *Past. pseudotuberculosis*, type II and/or IV, and the B- and/or D-subgroup of *Salmonella*. However, it is very probable that the severe gastroenteritis accompanied by damage to the liver parenchyma of a male patient, age 58, should be classified under this form. In this patient, an antibody titer to *Past. pseudotuberculosis*, type V was still demonstrated at 1:6,400 of serum dilution (Schmidt 1959, 1960).

b) Enteric Form: The clinical picture of this generally benign form corresponds to that of an acute and/or subacute but rarely to a chronic appendicitis. However, such a diagnosis is not confirmed surgically and/or histologically in most cases. Only in infrequent cases do the symptoms of a gastroenteritis with and without vomiting predominate.

The first, generally acute complaints are experienced in the mesogastric region or the lower right abdominal quadrant. The temperature is around 39-40°C. As in genuine appendicitis, the blood picture shows leukocytosis whereas the sedimentation rate is accelerated, in contrast to appendicitis (Lennert 1957). A clinically rapid and reliable delimitation of this form from genuine appendicitis by differential diagnosis is not yet possible.

Rapid diagnosis by means of antibody demonstration through slide agglutination at the bedside suggested by various authors (Christiansen 1957; Herrmann 1957; Girard et al 1959) cannot be recommended because of the unreliable results (spontaneous agglutination, cross reactions, etc.). The diagnostic value of the intracutaneous test with a filtered and carefully heated autolysate of *P. pseudotuberculosis*, type I recommended in recent years particularly by Mollaret (1961, 1962, 1963), also remains questionable. A positive reaction to this cutaneous test, the specificity of which is not yet adequately demonstrated, does not indicate whether the reaction of the patient means that he is suffering from the disease at the moment or suffered from an earlier infection by *Pasteurella*. This test consequently furnishes no information on the activity or inactivity of the infection. A negative reaction to this test does not exclude an acute infection as observations including demonstration of the pathogen by Mollaret (1961) and Baron et al (1961), have shown. In a case quoted by Mollaret, no answer could be given to the question whether the cutaneous reaction actually remained positive for 10 years or whether the cause of the positive reaction would have to be sought in a renewed and perhaps latent infection or in transverse reactions. Positive skin reactions in a child with tuberculosis and in individuals vaccinated against typhus were observed also by Mollaret (1961) when utilizing bacterial skin antigens but not with filtrates of autolysed bacteria. In our own experiments, guinea pigs sensitized with *salmonella typhosa* and/or *schottmuelleri* showed positive skin reaction with filtrates of cultures, treated by ultrasonics, of *P. pseudotuberculosis*, type II and IV.

Because of the uncertainty of diagnosis, surgery can generally not be avoided and we then find in the abdominal cavity varying amounts of a clear serous exudate. The mesenteric lymph nodes, especially in the ileo-caecal angle, are inflamed and enlarged. Painful tumoroid indurations, manifestations of a sub-ileus and ileus or a terminal ileitis may be the consequence, in individual cases, of the enlargement of the lymph nodes and/or the inflammation in the ileus and/or caecum (Graber and Knapp 1955; Berg and Hecker 1956; Graber 1956; Hecker 1957; Schmidt 1959; Knapp 1959; Brenner 1960; Krenmerer and Fuchs 1960; Muir 1960; Arnulf et al 1960; Baron et al 1961; Bonnet et al 1961; Gibel 1961; Joyeux et al 1961;

Katzmann 1962; Boettger 1962; Mollaret 1962, 1963) and may require in some infrequent cases an ileo-coecal resection (Graber and Knapp 1955, Berg and Hecker 1956; Masshoff 1962; Mollaret 1962, 1963). An erythema nodosum has also been observed in a few cases as a sign of hyperergic reaction (Morger 1962; Mollaret 1962).

Post-operative healing is quick and without complications as a rule so that an antibiotic therapy is not needed. Antibiotics should be given only for persisting or iterative abdominal complaints, for continuing gastroenteritic symptoms, in fever which does not recede or only very slowly, or when the antibody titer does not drop over a period of several weeks (Hecker 1957; Sander 1958; Knapp 1959, Mollaret 1962). In such cases, it is possible that an early and oriented antibiotic therapy with tetracycline (Knapp 1955) may prevent a transformation of the enteric into the septic-typhoidal form. Although no proof of such a transformation exists as yet, it would seem reasonable to assume this possibility.

According to Masshoff (1962), the septic-typhoidal and enteric forms of human pseudotuberculosis are distinguished from general infections with cyclic course and infectious alteration only by the degree of the type and extent of the organic manifestations. The pathogenic progress is assumed to be more closely related to typhus abdominalis than to tuberculosis (Graber and Knapp 1955; Graber 1956; Lennert 1961).

2) Frequency of Disease: Investigations in Germany and abroad between 1954 and 1958 (Knapp 1959) shows that efficient collaboration of the clinician, pathologist and microbiologist would indicate a greater incidence of infections in man by *P. pseudotuberculosis* than has been assumed so far. Other reports on the subject are available from Germany (Sander 1958, 1960; Schmidt 1959, 1960; Schoen et al 1960; Krennauer and Fuchs 1960; Edelhoff 1961; Gibel 1961; Paul and Rothermundt 1961; Boettger 1962; Katzmann 1962; Matsdorff 1962); Belgium (Callens et al 1961); Canada (Rhatko and Rodin 1962); Denmark (Frederiksen et al 1962); England (Mair et al 1960; Randall and Mair 1962); France (review of literature by Percebois 1961; Mollaret 1962, 1963, Gualda 1963); Netherlands (Daniels 1960, 1961, 1962, 1963); Yugoslavia (Guvelli 1962); Austria (Flamm et al 1958, 1960; Braun 1960; Brauner 1960); Switzerland (Beer 1960; Lindemann et al 1960; Morger 1962); and Czech-slovakia (Vortel 1958).

The cases published up to 1957 by Knapp (1959) had increased to 277 and/or 267 by early 1963. Table 1 groups them by the type of examination determining the diagnosis.

Table 1 - Observations of the Tübingen Institute of Hygiene

<u>Results of Examination</u>	<u>Total Cases</u>		
	<u>1954-57</u>	<u>1958-63</u>	<u>Total</u>
I - Demonstration of pathogen	15	10	25
II - Demonstration of antibody (characteristic histological findings)	81	59	140
III - Demonstration of antibodies (no histological examination or findings unknown)	13	84	97
IV - Demonstration of antibody (non-characteristic histological findings)	1	4	5
V - Antibodies not demonstrated (histological findings characteristic)	7	3	10
Total Cases/excl. V	<u>117/110</u>	<u>160/157</u>	<u>277/267</u>

If we assume the 10 cases listed under V in Table 1 as insufficiently clarified diagnostically, there remain 267 cases in which bacteriology confirmed the clinical-surgical and/or histopathological diagnosis of an infection with *P. pseudotuberculosis* by demonstration of the pathogen (25 patients) or was made very probable by the demonstration of antibodies. In the 10 patients, characteristic clinical, bioptic and histological findings permitted a preliminary diagnosis of the enteric form and differential diagnosis excluded tularemia, feline scabies or lymphogranuloma inguinal, without, however, being able to confirm the diagnosis through serological findings. In 4 and/or 6 patients, antibodies to *P. pseudotuberculosis*, type I were either not demonstrated at all or only at the very low titer of 1:20 to 1:40 of the serum dilution (Knapp 1959). Repeated examinations of the blood to control the titer curve was not possible with these patients for external reasons. The question whether such low titers to *P. pseudotuberculosis*, type I possess diagnostic significance can be answered only after a large observational material is available. The viewpoints on the question of a "limit titer" in literature by various authors are not uniform.

A breakdown of this larger statistical material by age and sex leads again to a confirmation of the first report that male adolescents primarily contract the benign form of human pseudotuberculosis. Our entire observational material is contrasted by 227 males as against 46 female patients. The sex of 4 patients had not been indicated. Two hundred four patients were between 6 and 18 years of age. The youngest patient was less than 1 year old and the two oldest patients were aged 35 and 39 respectively. No

indication of age was given for 19 patients. Similar observations have been reported recently by various authors, including specifically Mollaret (1960, 1962) with 30 and Daniels (1961, 1962, 1963) with 25 evaluated cases.

Grouped by season of the year, there were observed 79 cases in January through March, 78 in April through June, 49 in July through September, and 51 in October through December. A curve of monthly incidents of the disease would indicate a pronounced apex in late fall and winter and again in spring and early summer.

Hecker (1957) numbered among 20 patients 16 cases in November through March and only 4 patients in June. A similar seasonal grouping was observed by Mollaret (1962) in 30 cases described as pseudotuberculosis, not all of which are however, adequately confirmed in diagnosis by bacteriological-serological examination (Daniels 1962). Haenselt (1957), in 33 cases of purulent reticulocytary lymphadenitis established histologically (28 patients examined serologically showed 26 with antibodies to *P. pseudotuberculosis*), found a pronounced incidence of the disease especially in the months of April through June (we cannot here discuss the cases interpreted histologically as infection by *Pasteurella* but not examined bacteriologically and/or serologically or etiologically not sufficiently documented).

A satisfactory explanation for the seasonal incidence in man has not yet been found. More extensive investigations in the field of veterinary medicine on the seasonal incidence in animals (e.g. cats, guinea pigs, rabbits, birds, lap dogs, etc.) in specially frequent direct and/or indirect contact with man would here produce some information.

The question — important from the epidemiological viewpoint — whether patients in the country or in regular and/or frequent direct contact with animals are affected more frequently by pseudotuberculosis, is not reliably answered by the existing publications or our own observations. The respective statements by various authors in regard to this question are not documented by any exact findings from a sufficiently large experimental material. The possibility of contact infection is discussed in various communications (Greber and Knapp, 1955; Leduc et al 1959; Berthon and Mollaret 1960; Favre et al 1960; Mollaret 1960; Mair et al 1960; Lindemann et al 1960; Morger 1962; Daniels 1960, 1962; Matsdorf 1962; Mollaret and Berthon 1962; Randall and Mair 1962) on individual, sibling, community and/or group incidences having been in contact with sick and/or deceased animals (either concurrently or some days or weeks earlier) such as cats, gold hamsters, guinea pigs, birds and lap dogs, some of which showed antibodies to *P. pseudotuberculosis*. However, reliable confirmation of such contact infection is absent in all cases.

The low antibody titer (1:10) in a cat (Berthon and Mollaret 1960) is insufficient to regard it as the source of infection for children suffering from the enteric form. With the endemic existence of *P.*

pseudotuberculosis in many animals, even a positive reaction of the intrasutaneous test with a skin antigen of *P. pseudotuberculosis* does not permit any epidemiological conclusions.

So far only Daniels (1961, 1962) has been successful in the simultaneous demonstration of *P. pseudotuberculosis* in feces from a patient and from the canary of the latter. He regarded the bird as the source of infection for his patient whose antibody titer rose to 1:5,200. This first isolation of *P. pseudotuberculosis* from feces (Daniels 1921) in which Kampelmacher (1963) has also succeeded in the meantime, is a further indication for the enteric genesis of human pseudotuberculosis (Flamm and Kovacs 1958; Daniels 1961), in addition to the pathological findings.

II - Points on Laboratory Diagnosis

Knapp (1960) reported a few years ago in detail on the laboratory diagnosis of infections by *P. pseudotuberculosis*. We shall therefore, discuss briefly only a few of the points important for routine diagnostic which are, however, either not at all or not sufficiently considered.

1) Microscopic and Culture Demonstration of Pathogen:

a) The more intense staining of the poles (pole staining) indicated as characteristic for variety and again and again looked for in microscopic diagnosis of the pathogen is not constant and is therefore without significance for diagnosis (Girard 1942; Van Loghem 1946).

b) All strains are motile at 22-30°C. The U-flask designed by Baber (Knapp 1956), has been especially suitable for the demonstration of the motility of allegedly non-motile strains.

c) In an initial culture, some strains grow only at about 22°C (Knapp 1956; Mair et al 1960; Daniels 1961) and/or in an anaerobic milieu (Knapp and Marshoff 1954). It is therefore recommended to incubate the specimens in several cultures, both under aerobic and anaerobic conditions, at 22°C and 37°C. For isolation of *P. pseudotuberculosis* from feces (succeeded insofar only by Daniels (1961) and Kampelmacher (1963)) or other specimens from mixed infections, Daniels (1962) recommends citric desoxycholate agar according to Laifson, the importance of which for differential diagnosis between *P. Poutis* and *P. pseudotuberculosis* has already been pointed out by Thal and Chen (1955), and the selective medium for *Pasteurella* by Morris (1948).

2) Biochemical Investigation of Cultures: For biochemical differentiation of cultures of suspected strains, there should be used primarily the nutrient media and metabolic examinations which make possible at the same time differential-diagnostic delimitation against other varieties of *Pasteurella* and *Salmonella* (Knapp 1960, Mollaret 1961; Le Minor and Ben Hamida 1961; Mollaret and Le Minor 1962). Meyer et al (1963) recommend, in addition to the phage test, the following examinations grouped in

Table 2. The differential-diagnostic significance of the aesculin test was pointed out by Parnas (1961) and that of the β -galactosidase test by Le Minor and Mollaret (1961) and/or Mollaret and Le Minor (1962).

Table 2 - Biochemical Differential Diagnosis of Cultures

	<u>P. pseudo-</u> <u>tuberculosis</u>	<u>P. Pestis</u>	<u>P. Multocida</u>	<u>Salmonella</u>
Motility	+	-	-	+
melibiose	+	-	-	(\pm)
salicin	+ *	\pm	- *	-
sorbitol	\pm	- *	+	+
rhamnose	+	- *	-	\pm
sacharose	-	- *	+	-
aesculin	+	+	-	-
β - galactosidase	+	+	-	-
Urease	+	-	-	-
H ₂ S	\pm	-	+	+ *
indol	-	-	+ *	-

(*) - very infrequent exceptions.

3) Serological Investigations:

a) Antigen Analysis: The antigen analysis for strains of *P. pseudotuberculosis* is carried out by the technique customary for the diagnostic of *Salmonella*. In routine diagnostics, antigen analysis is restricted to the demonstration of the 5 thermostable, type-specific O-antigens of types I-IV described by Thal (1954), the H-antigen a common to types I, II, III and V of *P. pseudotuberculosis* and of the H-antigen b so far demonstrated only for type IV. Routine determination of the subtypes A and B known for types I and II (Schuette 1932) and type IV (Knapp 1960) has no diagnostic significance.

However, in all serological examinations, there is important the knowledge of the antigen characteristics common ("Partialantigengemeinschaft") to *P. pseudotuberculosis*, type II, and the O-factors 4 and/or 27 of subgroup B of *Salmonella* (Schuette 1932; Kauffman 1933; Knapp 1960) and to type IV and the O-factors 9.46 and/or 14 of the subgroups D and/or E of

Salmonella (Knapp 1956, 1960; Toucas and Girard 1956). Transverse serological reactions must be excluded by the utilization of saturated-type sera in the agglutination of the strains.

b) Demonstration of Antibodies: For the diagnosis of the enteric and of the septic-typhoidal form of human pseudotuberculosis, demonstration of antibodies is of particular importance because demonstration of the pathogen is possible only in infrequent cases. Antibodies are already present in most patients when the first clinical symptoms occur. Their demonstration can be easily made with the agglutination method which should be preferred to KHR (?) (Knapp 1957; Knapp and Stever 1956). Since O-antibodies are only infrequently demonstrated with boiled (sterilized ?) antigens (Knapp 1956, Daniels 1962; Mair 1963), agglutination should be carried out primarily with live or carefully killed test strains of type I-V. In contrast to the observations with types I, III and V, agglutination with test strains of type II and IV is non-specific because of their antigen relation to the subgroups B, D and H of Salmonella. Infections by types II and IV of *P. pseudotuberculosis* can be confirmed serologically only through the transverse saturation of the patient serum (Knapp 1956, 1960) which is necessary also if the test strains of Salmonella are not agglutinated in non-saturated patient serum (Daniels 1962). Several of the cases reported (Mollaret 1960, Favre et al 1960; Texier 1962; Rhatko et al 1962) as infections by types II and IV of strains of *P. pseudotuberculosis* do not satisfy these diagnostic prerequisites. In man, type-I infections are demonstrated primarily by serology. Infections confirmed through saturation of serum and/or demonstration of pathogen are less frequent for type II and even less frequent for type III and V (Knapp 1959, Daniels 1963). In all probability, strains of type IV of *P. pseudotuberculosis* are as little pathogenic for man (Knapp 1956; Daniels 1962) as for experimental animals (Thal 1954).

Communications on the demonstration of infections in man by strains of type IV should be accepted with reservations. In a few patients, the occurrence of incomplete antibodies was observed (Knapp 1956; Lindemann et al 1960).

4) Animal Experimentation: The choice animal for experimentation is the guinea pig. It should be remembered in animal experimentation that the virulence of the individual strains of the types I, II, III and V, pathogenic in guinea pigs, differs greatly and that most strains of type IV are apathogenic. Culture passages of the strains differ in the rapidity of decrease of virulence. Even if the pathogen has been demonstrated by culture, negative reaction must be expected in animal experimentation. Of interest is a personal communication of Purrows (1963) that he found a subculture of *P. pseudotuberculosis*, type IV (strain No. 32), to be pathogenic in guinea pigs.

5) Phage Test: Diagnosis of the pathogen is improved and accelerated (Knapp 1963) through a phage strain designated as "PST-phage" isolated from *P. pseudotuberculosis*. According to our investigations, this

strain reduced lysis (at differing intensity) in all strains of type I-V of *P. pseudotuberculosis* tested so far and also in strains of *P. pestis*. Bacterial strains of other varieties subject to lysis have so far not been observed by us but their demonstration can be expected in the individual case in parallel with the observations on the pest phages (Girard 1942, 1943). The property of producing lysis in bacteria of other varieties is possessed by strains of pest phages and their lytic action on *P. pseudotuberculosis* and strains of *Shigella* and *Coli* has been described repeatedly (Girard 1942, 1943; Gunnison et al., 1948, 1951; Knapp 1962, Mollaret 1962). Lysis of *P. pestis* by the PST-phage need not be considered in Europe for epidemiological reasons. No special methods are required to carry out the phage test.

Summary

The benign course of human pseudotuberculosis is found all over Europe. Any statements on the septic course can only be made if the antibody test in case of intestinal infections is carried out as a routine, with strains of *Past. pseudotuberculosis*, type I-V. One should attach a greater importance to the isolation of *Pasteurella* out of feces.

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